SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Levofloxacin Solution for Infusion 500 mg/100ml –Nirliv

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sr.No.	MaterialName	Quantity per 100 ml
		Quantity
1	LevofloxacinHemihydrate	500 mg
2	Sodium ChlorideBP	
3	Di-Sodium EDTABP	
4	Hydrochloric AcidBP	
5	Water for InjectionsBP	

3. PHARMACEUTICAL FORM

Solution for infusion

Levofloxacin Solution for infusion is a clear and greenish-yellow colour solution with pH 3.8 to 5.8 and osmolality ranging from 270 to 340 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Levofloxacin solution for infusion is indicated in adults for the treatment of the following infections (see sections 4.4 and 5.1):

- Acute pyelonephritis and complicated urinary tract infections (see section 4.4)
- Chronic bacterial prostatitis
- Inhalation Anthrax: post exposure prophylaxis and curative treatment (see section 4.4).

In the below-mentioned infections levofloxacin should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.

- Community-acquired pneumonia
- Complicated skin and soft tissue infections.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Levofloxacin solution for infusion is administered by slow intravenous infusion once or twice daily. The dosage depends on the type and severity of the infection and the susceptibility of the presumed causative pathogen. Treatment with Levofloxacin after initial use of the intravenous preparation may be completed with an appropriate oral presentation according to the SPC for the film-coated tablets and as considered appropriate for the individual patient. Given the bioequivalence of the parenteral and oral forms, the same dosage can be used

Posology.

The following dose recommendations can be given for levofloxacin

Dosage in patients with normal renal function (creatinine clearance> 50 ml/min)

Indication	**Daily dose regimen** (according to severity)	**Totaldurationoftreatment** [1](according to severity)
Community-acquired pneumonia	500 mg once or twice daily	7 - 14 days
Acute pyelonephritis	500 mg once daily	7 - 10 days
Complicated urinary tract infections	500 mg once daily	7 - 14 days
Chronic bacterial prostatitis	500 mg once daily	28 days
Complicated skin and soft tissue infections	500 mg once or twice daily	7 - 14 days
Inhalation anthrax	500 mg once daily	8 weeks

Treatment duration includes intravenous plus oral treatment. The time to switch from intravenous to oral treatment depends on the clinical situation but is normally 2 to 4 days.

Special populations

Impaired renal function (creatinine clearances 50 ml/min)

Dose regimen

	250 mg/24 h	**500 mg/24 h**	**500 mg/12 h**
Creatinine clearance	first dose: 250 mg	first dose: 500 mg	first dose: 500mg
50 - 20 ml/min	then: 125 mg/24 h	then: 250 mg/24 h	then: 250 mg/12 h

19-10 ml/min	then: 125 mg/48 h	then: 125 mg/24 h	then: 125 mg/12 h
< 10 ml/min (includinghaemodialysisandCAPD)[1]	then: 125 mg/48 h	then: 125 mg/24 h	then: 125 mg/24 h

No additional doses are required after haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

Impaired liverfunction

No adjustment of dose is required since levofloxacin is not metabolised to any relevant extent by the liver and is mainly excreted by the kidneys.

Elderly population

No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal function (see section 4.4 'Tendonitis and tendon rupture" and "QT interval prolongation").

Paediatric population

Levofloxacin is contraindicated in children and growing adolescents (see section 4.3).

Method of administration

Levofloxacin solution for infusion is only intended for slow intravenous infusion; it is administered once or twice daily. The infusion time must be at least 30 minutes for 250 mg or 60 minutes for 500 mg levofloxacin solution for infusion (see section 4.4).

For incompatibilities see section 6.2 and compatibility with other infusion solutions see section 6.6.

4.3 Contraindications

Levofloxacin solution for infusion must not be used:

- in patients hypersensitive to levofloxacin or any other quinolone or any of the excipients listed in section 6.1,
- in patients with epilepsy,
- in patients with history of tendon disorders related to fluoroquinolone administration,
- in children or growing adolescents,
- during pregnancy,
- in breastfeeding women.

4.4 Special warnings and precautions for use

The use of levofloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with levofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3).

Risks of resistance

Methicilin-resistant S. aureus are very likely to possess co-resistance to fluoroquinolones, including levofloxacin. Therefore, levofloxacin is not recommended for the treatment of known or suspected MRSA infections unless laboratory results have confirmed susceptibility of the organism to levofloxacin (and commonly recommended antibacterial agents for the treatment of MRSA-infections are considered inappropriate).

Resistance to fluoroquinolones of E. coli - the most common pathogen involved in urinary tract infections - varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in E. coli to fluoroquinolones.

Inhalation Anthrax

Use in humans is based on in vitro Bacillus anthracis susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. Levofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

Infusion Time

The recommended infusion time of at least 30 minutes for 250 mg or 60 minutes for 500 mg Levofloxacin solution for infusion should be observed. It is known for ofloxacin that during infusion tachycardia and a temporary decrease in blood pressure may develop. In rare cases, as a consequence of a profound drop in blood pressure, circulatory collapse may occur. Should a conspicuous drop in blood pressure occur during infusion of levofloxacin, (l-isomer of ofloxacin) the infusion must be halted immediately.

Tendonitis and tendon rupture

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, patients receiving daily doses of 1000 mg, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with levofloxacin should be discontinued, and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

Clostridium difficile-associated disease

Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with Levofloxacin (including several weeks after treatment), may be symptomatic of Clostridium difficile-associated disease (COAD). COAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis (see section 4.8). It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treatment with levofloxacin. If COAD is suspected or confirmed, levofloxacin should be stopped immediately and appropriate treatment initiated without delay. Anti-peristaltic medicinal products are contraindicated in this clinical situation.

Patients predisposed to seizures

Quinolones may lower the seizure threshold and may trigger seizures. Levofloxacin is contraindicated in patients with a history of epilepsy (see section 4.3) and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures or concomitant treatment with active substances that lower the cerebral seizure threshold, such as theophylline (see section 4.5). In case of convulsive seizures (see section 4.8), treatment with levofloxacin should be discontinued.

Patients with G-6- phosphate dehydrogenase deficiency

Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents. Therefore, if levofloxacin has to be used in these patients, potential occurrence of haemolysis should be monitored.

Patients with renal impairment

Since levofloxacin is excreted mainly by the kidneys, the dose of Levofloxacin solution for infusion should be adjusted in patients with renal impairment (see section 4.2).

Hypersensitivity reactions

Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up to anaphylactic shock), occasionally following the initial dose (see section 4.8). Patients should discontinue treatment immediately and contact their physician or an emergency physician, who will initiate appropriate emergency measures.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN: also known as Lyell's syndrome), Stevens Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with levofloxacin (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions, and be closely monitored. If signs and symptoms suggestive of these reactions appear, levofloxacin should be discontinued immediately and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of levofloxacin, treatment with levofloxacin must not be restarted in this patient at any time.

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, occurring more frequently in the elderly, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g., glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see section 4.8).

Levofloxacin treatment should be stopped immediately if a patient reports blood glucose disturbance and alternative nonfluoroquinolone antibacterial therapy should be considered.

Prevention of photosensitisation

Photosensitisation has been reported with levofloxacin (see section 4.8). It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), during treatment and for 48 hours following treatment discontinuation in order to prevent photosensitisation.

Patients treated with Vitamin K antagonists

Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly (see section 4.5).

Psychotic reactions

Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In very rare cases these have progressed to suicidal thoughts and self-

endangering behaviour - sometimes after only a single dose of levofloxacin (see section 4.8). In the event that the patient develops these reactions, levofloxacin should be discontinued immediately at the first signs or symptoms of these reactions and patients should be advised to contact their prescriber for advice. Alternative nonfluoroquinolone antibacterial therapy should be considered, and appropriate measures instituted. Caution is recommended if levofloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.

QT interval prolongation

Caution should be taken when using fluoroquinolones, including levofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:

- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and Ill antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).
- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including levofloxacin, in these populations. (See section 4.2 Elderly, 4.5, 4.8, and 4.9).

Peripheral neuropathy

Cases of sensory or sensory motor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with levofloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition (see section 4.8).

Hepatobiliary disorders

Cases of hepatic necrosis up to fatal hepatic failure have been reported with levofloxacin, primarily in patients with severe underlying diseases, e.g. sepsis (see section 4.8). Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

Exacerbation of myasthenia gravis

Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Post marketing serious

adverse reactions, including deaths and the requirement for respiratory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Levofloxacin is not recommended in patients with a known history of myasthenia gravis.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see sections 4.7 and 4.8).

Superinfection

The use of levofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Interference with laboratory test

In patients treated with levofloxacin, determination of opiates in urine may give false-positive results. It may be necessary to confirm positive opiate screens by more specific method.

Levofloxacin may inhibit the growth of Mycobacterium tuberculosis and, therefore, may give false-negative results in the bacteriological diagnosis of tuberculosis.

Aortic aneurysm and dissection, and heart valve regurgitation/incompetence

Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.8).

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease or congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection or heart valve disease, or in presence of other risk factors or conditions predisposing:

- for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Becet's disease, hypertension, rheumatoid arthritis) or additionally
- for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjogren's syndrome) or additionally
- for heart valve regurgitation/incompetence (e.g. infective endocarditis).

The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

Levofloxacin solution for infusion contains sodium

This medicinal product contains 354 mg sodium per 100 ml equivalent to 17.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Levofloxacin solution for infusion is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal Products on levofloxacin

Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs

No pharmacokinetic interactions of levofloxacin were found with theophylline in a clinical study. However, a pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, non- steroidal anti-inflammatory drugs, or other agents which lower the seizure threshold.

Levofloxacin concentrations were about 13% higher in the presence of fenbufen than when administered alone.

Probenecid and cimetidine

Probenecid and cimetidine had a statistically significant effect on the elimination of levofloxacin. The renal clearance of levofloxacin was reduced by cimetidine (24%) and probenecid (34%). This is because both drugs are capable of blocking the renal tubular secretion of levofloxacin. However, at the tested doses in the study, the statistically significant kinetic differences are unlikely to be of clinical relevance.

Caution should be exercised when levofloxacin is coadministered with drugs that affect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Other relevant information

Clinical pharmacology studies have shown that the pharmacokinetics of levofloxacin were not affected to any clinically relevant extent when levofloxacin was administered together with the

following drugs: calcium carbonate, digoxin, glibenclamide, ranitidine.

Effect of levofloxacin on other medicinal Products

Ciclosporin

The half-life of ciclosporin was increased by 33% when coadministered with levofloxacin.

Vitamin K antagonists

Increased coagulation tests (PT/INR) and/or bleeding, which may be severe, have been reported in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin). Coagulation tests, therefore, should be monitored in patients treated with vitamin K antagonists (see section 4.4)

Drugs known to prolong QT interval

Levofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and Ill antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4 QT interval prolongation).

Other relevant information

In a pharmacokinetic interaction study, levofloxacin did not affect the pharmacokinetics of theophylline (which is a probe substrate for CYP1A2), indicating that levofloxacin is not a CYP1A2 inhibitor.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of levofloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

However, in the absence of human data and due to that experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in pregnant women (see sections 4.3 and 5.3).

Breastfeeding

Levofloxacin is contraindicated in breastfeeding women. There is insufficient information on the excretion of levofloxacin in human milk; however, other fluoroquinolones are excreted in breast milk. In the absence of human data and due to that experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in breastfeeding women (see sections 4.3 and 5.3).

Fertility

Levofloxacin caused no impairment of fertility or reproductive performance in rats.

4.7 Effects on ability to drive and use machines

Levofloxacin has minor or moderate influence on the ability to drive and use machines. Some undesirable effects (e.g. dizziness/vertigo, drowsiness, visual disturbances) may impair the patient's ability to concentrate and react, and therefore may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

4.8 Undesirable effects

The information given below is based on data from clinical studies in more than 8300 patients and on extensive post marketing experience.

Frequencies in this table are defined using the following convention: very common (1/10), common (1/100, <1/10), uncommon (1/1000, <1/100), rare (1/10000, <1/1000), very rare (<1/10000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table of adverse reactions

System organ class	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to<1/100)**	**Rare (≥1/10,000 to<1/1,000)**	**Notknown (cannot beestimated from availabledata)**
Infections andinf estations		Fungal infection including Candida infection Pathogen resistance.		
Blood andthe lymphaticsystem disorders		Leukopenia Eosinophilia.	Thrombocytopenia Neutropenia.	Pancytopenia Agranulocytosis Haemolyticanaemia.
Immune systemDi sorders			Angioedema Hypersensitivity(sees ection4.4).	Anaphylactic shock[a] Anaphylactoidshock [a] (see section4.4).
Endocrine disorders			Syndrome of inappropriatesecretio n of antidiuretic hormone(SIADH).	

Metabolism and nutrition disorders		Anorexia	Hypoglycaemia particularly in diabetic patients, Hypoglycaemic coma (see section 4.4).	Hyperglycaemia (see section 4.4)
Psychiatric Disorders*	Insomnia	Anxiety Confusional state Nervousness	Psychotic reactions (with e.g. hallucination, paranoia) Depression Agitation Abnormal dreams Nightmares, Delirium.	Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt (see section 4.4).
Nervous system Disorders*	Headache Dizziness	Somnolence Tremor Dysgeusia	Convulsion (see sections 4.3 and 4.4) Paraesthesia, Memory impairment.	Peripheral sensory neuropathy (see section 4.4), Peripheral sensory motor neuropathy (see section 4.4), Parosmia including anosmia, Dyskinesia Extrapyramidal disorder Ageusia, Syncope, Benign intracranial hypertension.
Eye disorders*			Visual disturbances such as blurred vision (see section 4.4)	Transient vision loss (see section 4.4), uveitis.
Ear and Labyrinth disorders*		Vertigo	Tinnitus	Hearing loss Hearing impaired.

Cardiac Disorders**			Tachycardia, Palpitation	Ventricular tachycardia, which may result in cardiac arrest Ventricular arrhythmia and torsade de pointes (reported predominantly in patients with risk factors of QT prolongation), electrocardiogram QT prolonged (see sections 4.4 and 4.9).
Vascular Disorders**	Applies to iv form only: Phlebitis.		Hypotension	
Respiratory, thoracic and mediastinal disorders.		Dyspnoea		Bronchospasm Pneumonitis allergic.
Gastro-intestinal disorders	Diarrhoea Vomiting Nausea	Abdominal pain Dyspepsia Flatulence Constipation		Diarrhoea-haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis (see section 4.4) Pancreatitis.
Hepatobiliary disorders	Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT).	Blood bilirubin increased		Jaundice and severe liver injury, including fatal cases with acute liver failure, primarily in patients with severe underlying diseases (see section 4.4), Hepatitis.

Skin and subcutaneous tissue disorders [b]		Rash, Pruritus, Urticaria Hyperhidrosis	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see section 4.4), Fixed drug eruption	Toxicepidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Photosensitivity reaction (see section 4.4) Leukocytoclastic vasculitis, Stomatitis.
Musculoskeletal and connective tissue disorders*		Arthralgia Myalgia	Tendon disorders (see sections 4.3 and 4.4) including tendinitis (e.g. Achilles tendon) Muscular weakness which may be of special importance in patients with myasthenia gravis (see section 4.4).	Rhabdomyolysis Tendon rupture (e.g. Achilles tendon) (see sections 4.3 and 4.4) Ligament rupture, Muscle rupture, Arthritis.
Renal and Urinary disorders		Blood creatinine increased	Renal failure acute (e.g. due to interstitial nephritis).	
General disorders and administration site conditions*	Applies to iv form only: Infusion site reaction (pain, reddening).	Asthenia	Pyrexia	Pain (including pain in back, chest, and extremities).

Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose

[b]Mucocutaneous reactions may sometimes occur even after the first dose

Other undesirable effects which have been associated with fluoroquinolone administration include:

- attacks of porphyria in patients with porphyria.

* Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory

impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see Section 4.4).

** Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at info@aculife.com

4.9 Overdose

According to toxicity studies in animals or clinical pharmacology studies performed with supra-therapeutic doses, the most important signs to be expected following acute overdose of Levofloxacin Solution for infusion are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval.

CNS effects including confusional state, convulsion, hallucination, and tremor have been observed in post marketing experience.

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Haemodialysis, including peritoneal dialysis and CAPO, are not effective in removing levofloxacin from the body. Nospecific antidote exists.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: - quinolone antibacterials, fluoroquinolones **ATC code:** J01MA12

Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S (-) enantiomer of the racemic drug substance ofloxacin.

Mechanism of action

As a fluoroquinolone antibacterial agent, levofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.

PK/PD relationship

The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum (Cmax) or the area under the curve (AUG) and the minimal inhibitory concentration (MIC).

Mechanism of resistance

Resistance to levofloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNA gyrase and topoisomerase IV. Other resistance mechanisms such as permeation barriers (common in Pseudomonas aeruginosa) and efflux mechanisms may also affect susceptibility to levofloxacin.

Cross-resistance between levofloxacin and other fluoroquinolones is observed. Due to the mechanism of action, there is generally no cross-resistance between levofloxacin and other classes of antibacterial agents.

Breakpoints

The EUCAST recommended MIC breakpoints for levofloxacin, separating susceptible from susceptible increased exposure organisms and susceptible increased exposure from resistant organisms are presented in the below table for MIC testing (mg/I).

EUCAST clinical MIC breakpoints for levofloxacin (Version 10.0; 2020-01-01):

Pathogen	**Susceptible**	**Resistant**
Enterobacterales	≤0.5mg/l	>1 mg/I
Pseudomonas spp.	≤0.001 mg/I	>1 mg/I
Acinetobacter spp.	≤0.5 mg/I	>1 mg/I
Staphylococcus aureus Coagulase-negative staphylococci	≤0.001 mg/I	>1 mg/I
Enterococcusspp[1]	≤4 mg/I	>4 mg/I
Streptococcus pneumoniae	≤0.001 mg/I	>2 mg/I
Streptococcus groups A, B, C and G	≤0.001 mg/I	>2 mg/I
Haemophllusinfluenzae	≤0.06 mg/I	>0.06 mg/I
Moraxella catarrhalis	≤0.125 mg/I	>0 .125 mg/I
He/icobacterpylori	≤1 mg/I	>1 mg/I
Aerococcussanguinicolaand urinae[2]	≤2 mg/I	>2 mg/I
Aeromonasspp.	S0.5 mg/I	>1 mg/I
PK-PD (Non-species related) breakpoints	S0.5 mg/I	>1 mg/I

1: uncomplicated urinary tract infections only

2: Susceptibility can be inferred from ciprofloxacin susceptibility

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species

Aerobic Gram-positive bacteria

Bacillus anthracis

Staphylococcus aureusmethicillin-susceptible

Staphylococcus saprophyticus

Streptococci, group C and G

Streptococcus agalactiae

Streptococcus pneumoniae

Streptococcus pyogenes

Aerobic Gram- negative bacteria

Eikenellacorrodens

Haemophilus influenza

Haemophilus para-influenzae

Klebsiellaoxytoca

Moraxella catarrhalis

Pasteurellamultocida

Proteusvulgaris

Providencia rettgeri

Anaerobic bacteria

Peptostreptococcus

Other

Chlamydophila pneumoniae

Chlamydophilapsittaci

Chlamydia trachomatis

Legionella pneumophila

Mycoplasma pneumoniae

Mycoplasma hominis

Ureaplasmaurealyticum

Species for which acquired resistance may be a Problem
Aerobic Gram-Positive bacteria
Enterococcus faecalis
Staphylococcus aureus methicillin-resistant#
Coagulase negative Staphylococcusspp
Aerobic Gram- negative bacteria
Acinetobacter baumannii
Citrobacterfreundii
Enterobacter aerogenes
Enterobactercloacae
Escherichia coli
Klebsiella pneumonia
Morganellamorganii
Proteus mirabilis
Providencia stuartii
Pseudomonas aeruginosa
Serratiamarcescens
Anaerobic bacteria
Bacteroidesfragilis
Inherently Resistant Strains
Aerobic Gram-Positive bacteria
Enterococcus faecium

Methicillin-resistant S. aureus are very likely to possess co-resistance to fluoroquinolones, including levofloxacin.

5.2 Pharmacokinetic properties

Absorpition

Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1 - 2 h. The absolute bioavailability is 99 - 100 %. Food has little effect on the absorption of levofloxacin.

Steady state conditions are reached within 48 hours following a 500 mg once or twice daily dosage regimen.

Distribution

Approximately 30 - 40 % of levofloxacin is bound to serum protein. The mean volume of distribution of levofloxacin is approximately 100 I after single and repeated 500 mg doses, indicating widespread distribution into body tissues.

Penetration into tissues and body fluids:

Levofloxacin has been shown to penetrate into bronchial mucosa, epithelial lining fluid, alveolar macrophages, lung tissue, skin (blister fluid), prostatic tissue and urine. However, levofloxacin has poor penetration into cerebra-spinal fluid.

Biotransformation

Levofloxacin is metabolized to a very small extent, the metabolites being desmethyl-levofloxacin and levofloxacin N- oxide. These metabolites account for < 5 % of the dose excreted in urine. Levofloxacin is stereochemically stable and does not undergo chiral inversion.

Elimination

Following oral and intravenous administration of levofloxacin, it is eliminated relatively slowly from the plasma ($\mathbf{t}_{½}$, 6 – 8 h). Excretion is primarily by the renal route (> 85 % of the administered dose).

The mean apparent total body clearance of levofloxacin following a 500 mg single dose was 175 +/-29.2 ml/min.

There are no major differences in the pharmacokinetics of levofloxacin following intravenous and oral administration, suggesting that the oral and intravenous routes are interchangeable.

Linearity.

Levofloxacin obeys linear pharmacokinetics over a range of 50 to 1000 mg

Special Populations

Subjects with renal insufficiency

The pharmacokinetics of levofloxacin are affected by renal impairment. With decreasing renal function renal elimination and clearance are decreased, and elimination half-lives increased as shown in the table below:

Pharmacokinetics in renal insufficiency following single oral 500 mg dose

Cl_{cr} [ml/min]	<20	20-49	50 - 80
CI_R [ml/min]	13	26	57
$t_{1/2}$ [h]	35	27	9

Elderly subjects

There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects, except those associated withdifferences in creatinine clearance.

Gender differences

Separate analysis for male and female subjects showed small to marginal gender differences in levofloxacin pharmacokinetics. There is no evidence that these gender differences are of clinical relevance.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential and toxicity to reproduction anddevelopment.

Levofloxacin caused no impairment of fertility or reproductive performance in rats and its only effect on fetuses was delayed maturation as a result of maternal toxicity.

Levofloxacin did not induce gene mutations in bacterial or mammalian cells but did induce chromosome aberrations in Chinese hamster lung cells in vitro. These effects can be attributed to inhibition of topoisomerase II. In vivo tests (micronucleus, sister chromatid exchange, unscheduled DNA synthesis, dominant lethal tests) did not show any genotoxic potential.

Studies in the mouse showed levofloxacin to have phototoxic activity only at very high doses. Levofloxacin did not show any genotoxic potential in a photomutagenicity assay, and it reduced tumour development in a photocarcinogenity study.

In common with other fluoroquinolones, levofloxacin showed effects on cartilage (blistering and cavities) in rats and dogs. These findings were more marked in young animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Edetate Disodium

Sodium chloride

Hydrochloric acid

Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with heparin or alkaline solutions (e.g. sodium bicarbonate). This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Shelf life as packaged for sale: 24 months

Shelf life after removal of the outer carton - to be used immediately

From a microbiological point of view, the solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store below 30ºC. Do not freeze.

Keep bottle in the outer carton in order to protect from light (see section 6.3). Inspect visually prior to use. Only clear solutions without particles should be used.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

100 ml plastic bottle kept in carton with pack insert.

6.6 Special precautions for disposal <and other handling>

No protection from light is necessary during infusion. For single use only. Discard any unused solution.

As for all medicines, any unused medicinal product should be disposed of accordingly and in compliance with local environmental regulations.

Mixture with other solutions for infusion:

Levofloxacin Solution for infusion is compatible with the following solutions for infusion:

0.9 % sodium chloride solution USP.

5 % dextrose injection USP.

2.5 % dextrose in Ringer solution.

Combination solutions for parenteral nutrition (amino acids, carbohydrates, electrolytes).

See section 6.2 for incompatibilities.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

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Date: 12.07.2023